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Molecular marker identifies normal stem cells as intestinal tumor source

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Scientists at St. Jude Children's Research Hospital have answered a central question in cancer biology: whether normal stem cells can give rise to tumors. Stem cells are immature cells that can renew themselves and give rise to mature differentiated cells that compose the range of body tissues. In recent years, researchers have developed evidence that cancers may arise from mutant forms of stem cells.

Like a brand-name product instantly identifiable by its trademarked logo, normal and cancerous stem cells display on their surface characteristic proteins, including Prominin1 or CD133. A key question in cancer biology has been whether these so-called cancer stem cells arise from normal stem cells or more mature cancer cells that somehow reacquire the characteristics of stem cells.

In the advanced, online issue of the journal *Nature*, St. Jude investigators show that Prominin1 marks normal intestinal stem cells and that these cells, when mutated, give rise to intestinal tumors. The finding could also aid in identifying the source of cancer stem cells in the lung, kidney, brain, pancreas and other tissues.

"The idea that cancers might arise from mutant stem cells is an attractive one; but until now the link between normal and cancer stem cells in solid tissues like the intestine was not known," said Richard Gilbertson, M.D., Ph.D., associate member of the St. Jude Developmental Neurobiology and Oncology departments and the paper's senior author. "Our work provides the first direct link between normal solid tissue stem cells and

cancer. The fact that this occurs in the intestine is particularly interesting since human intestinal tumors contain Prominin1-expressing cancer stem cells."

In addition to providing insights into the origins of cancer, the work might help scientists identify more effective treatments. "Normal stem cells are designed to withstand environmental insults," Gilbertson said. "Thus cancer stem cells might use these same mechanisms to resist chemotherapy and radiotherapy. Remnant cancer stem cells might therefore cause tumors to relapse and re-grow following treatment. If we could kill these cancer stem cells, we might be able to prevent relapse. Understanding the link between normal and cancerous stem cells should help us target the latter while preserving the former."

Working with mice, the researchers inserted a genetic switch that enabled them to selectively turn on a colored tracer molecule only in cells that were expressing, or had expressed, Prominin1. These tracer experiments revealed that Prominin1 cells generate the covering of the entire small intestine and are therefore the stem cell of this tissue.

Next, the researchers switched on cancer-producing machinery in the Prominin1 intestinal stem cells and used a fluorescent tracer to follow the offspring of these cells. Those studies revealed that the stem cells stopped making normal intestine and made tumors instead. "We saw a dramatic change in these laboratory models," Gilbertson said. "The tumorous tissue ultimately replaced the entire normal intestine. In terms of clinical importance, now that we have isolated both the normal, parental stem cells and the cancer stem cells, we can begin screening compounds that will affect the malignant stem cell but not the normal stem cell."

More broadly, Prominin1 might prove to be a useful marker to trace cancer stem cells in the kidney, brain, pancreas and other tissues. The

researchers are also exploring the use of stem cell markers in diseases other than cancer. "As we develop these kinds of characteristic markers for stem cells, we might be able to use them to isolate stem cells capable of regenerating healthy tissue in patients who suffer diabetes or other diseases due to organ failure," Gilbertson said.

Source: St. Jude Children's Research Hospital